Organic Process Research & Development **2007**, *11,* 341−345

# An Improved Manufacturing Process for the Antimalaria Drug Coartem. Part II

Ulrich Beutler, Peter C. Fuenfschilling,* and Andreas Steinkemper

*Novartis Pharma AG, Chemical and Analytical Development, CH-4002 Basel, Switzerland*

## Abstract:

**The manufacturing process for lumefantrine, 2, one of the two active principles in the fixed-dose combination of the antimalarial drug Coartem, was reworked. For the conversion of 2-chloro-1-(2,7-dichloro-9H-fluoren-4-yl)ethanone, 5, to 2-dibutylamino-1-(2,7-dichloro-9H-fluoren-4-yl)ethanol, 8, a one-pot process was developed that eliminated isolation of the epoxide 2-(2,7-dichloro-9H-fluoren-4-yl)oxirane, 7. Significant increase in throughput was achieved by applying new reaction and crystallization conditions for the Knoevenagel condensation of 2-dibutylamino-1-(2,7-dichloro-9H-fluoren-4-yl)ethanol, 8, to 2-dibutylamino-1-{2,7-dichloro-9-[1-(4-chlorophenyl)meth-(*Z*)-ylidene]-9H-fluoren-4-yl}ethanol, 2.**

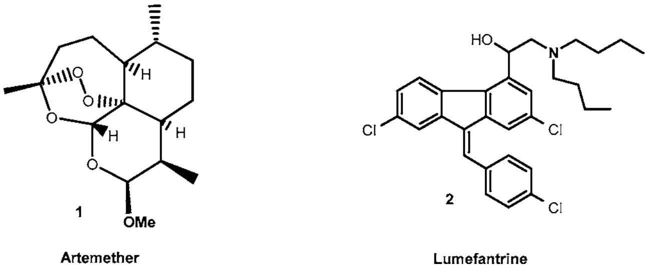
## 1. Introduction

Coartem is the only fixed-dose combination medicine combining artemether, **1**, an artemisinin derivative, and lumefantrine, **2** (Figure 1). This fixed-dose combination is of great benefit to patients as it facilitates treatment compliance and supports optimal clinical effectiveness. In the preceding paper,[1] the redesign of the manufacturing process for the natural product derivative **1** was described. In this paper, we present our results on the improvement of the manufacturing process for lumefantrine, **2**.

Since in the fixed-dose combination the racemic compound lumefantrine is the dominant[2] component, the demand figures for this compound amounted to several hundred tons annually. Thus, in parallel to our investigation on artemether, we set up a program aimed at lowering the manufacturing costs of lumefantrine by improving the overall yield and, in particular, by increasing the throughput.

## 2. Current Manufacturing Procedure for 2

The current process for the manufacture of **2** is outlined in Scheme 1. It starts with the chlorination of 9H-fluorene in acetic acid at 40 °C, a process which is not selective. In addition to the desired 2,7-isomer **4**, large amounts of 2,5-dichloro-9H-fluorene together with monochlorinated and trichlorinated compounds are also formed. However, by applying controlled[3] crystallization conditions, compound **4** can be isolated in pure form.



1

2

*Figure 1.* **Active ingredients of Coartem: artemether 1 and lumefantrine 2.**

The chloroacylation of **4** is performed by adding a solution of **4** in dichloromethane at 0−5 °C to a suspension of aluminum chloride and chloroacetyl chloride in dichloromethane. The reaction mixture is quenched with diluted hydrochloric acid, and after phase separation and washing, dichloromethane is distilled off and replaced by ethanol. The reaction mass is cooled to 20 °C, and compound **5** is isolated in 94% yield[4] by filtration and drying.

In the conversion of **5** to **7**, the intermediate chlorohydrin **6** is not isolated but is instead converted in situ to epoxide **7**. The reduction is run at 0 °C by adding sodium borohydride to a suspension of **5** in ethanol. Excess of sodium borohydride is then destroyed by heating the reaction mixture for 2 h at 55 °C.[5] Sodium methylate is added in portions, and after stirring for another hour at 55 °C, the reaction mixture is cooled to 0 °C and **7** is isolated in 86% yield by filtration and drying. Ring opening is achieved by heating epoxide **7** with an excess of dibutylamine in ethanol at 78 °C for at least 15 h. The mixture is cooled to 0 °C, and compound **8** is isolated by filtration and drying. Converting **8** via a Knoevenagel-type condensation leads to the *E*/*Z*-isomers **9** and **2**, respectively. From this mixture, the desired *Z*-isomer **2** is isolated by taking advantage of the rapid equilibrium between the two isomers.[6] The manufacturing process is completed by the recrystallization of crude **2** from 2-propanol.[7a−c]

When reviewing the whole process for potential improvements, the poor yield in the chlorination step seemed to be the most promising starting point. However, after it was found that simply altering the chlorination conditions has no significant effect on the selectivity, we decided to retain the current process conditions for this step. Fluorene is a low-cost starting material, and since this step occurs at the

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* To whom correspondence should be addressed. E-mail: peter.fuenfschilling@balcab.ch.

(1) Boehm, M.; Fuenfschilling, P. C.; Krieger, M.; Kuesters, E.; Struber, F. *Org. Process Res. Dev.* **2007**, *11*, 336−340.

(2) The fixed-dose combination contains 20 mg of **1** and 120 mg of **2**.

(3) For details, see Experimental Section.

(4) As the main by-product, 3-chloroacetyl-2,7-fluorene can be detected in the mother liquor. At higher reaction temperature, bichloroacylated products are formed also.

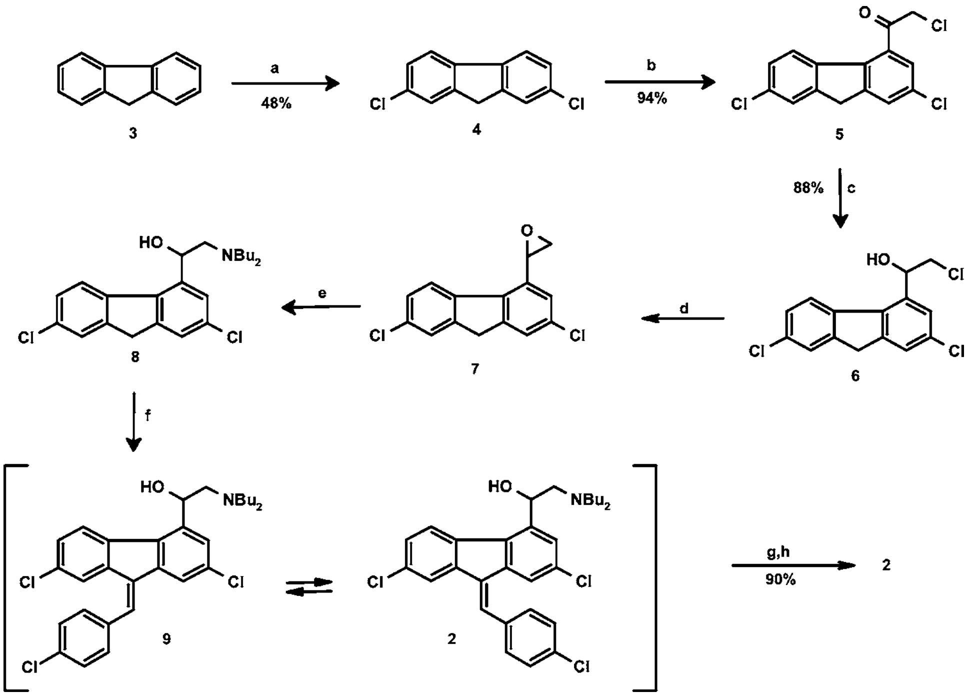
(5) With the increase in temperature, a strong release of hydrogen takes place.

(6) If pure **2** is heated at 70 °C in the reaction media of the condensation reaction, the equilibrium is reached within a few hours.

(7) (a) Rao, D. R.; Kankan, R. N.; Phull, M. S. Patent Application CN 1009-3724 20060424, 2005. (b) Deng, R.; Zhong, J.; Zhao, D.; Wang, J.; Yaoxue, X. **2000**, *35* (1), 22. (c) Allmendinger, Th.; Wernsdorfer, W. H. PCT WO 99/67197.

10.1021/op060244p CCC: $37.00

***Scheme 1.*** **Current manufacturing process of 2**[a]



[a] Reagent and conditions: (a) $Cl_2$, AcOH, 40 °C; (b) $ClCH_2COCl$, $AlCl_3$, $CH_2Cl_2$, 0−5 °C; (c) $NaBH_4$, EtOH, 0−5 °C; (d) NaOMe, 50−60 °C; (e) dibutylamine, EtOH, 78 °C, 15 h; (f) *p*-chlorobenzaldehyde, NaOH, EtOH; (g) isolation of crude **2** by crystallization, 38 °C, 24 h; (h) recrystallization from 2-propanol.

start of the synthesis, the low yield could be tolerated. Because of this cost argument, we also did not consider switching to *N*-chlorosuccinimide as the chlorination agent, nor to acetonitrile as the reaction solvent.[8]

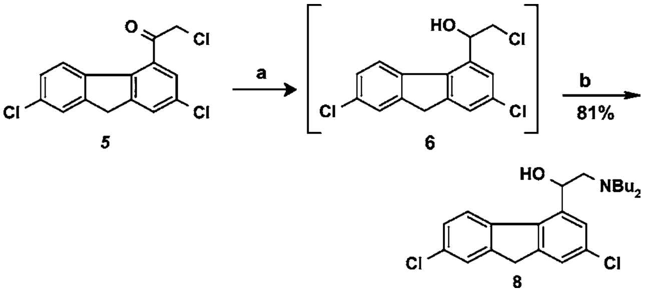
In view of the excellent yield and throughput for the chloroacylation **4** → **5**, we also saw no reason to try to improve this step. Thus, we decided to concentrate our efforts on improving the remaining steps of the synthesis. In particular, we wanted to eliminate the isolation of epoxide **7** (for both throughput and occupational hygiene reasons) and to improve the throughput in the conversion **8** → **2**. In the Knoevenagel condensation reaction, the cycle time was lengthy, and in the final crystallization, the concentration was far from that of an ideal production process (vide infra).

## 3. Redesign of the Manufacturing Process for 2

**3.1. Development of a One-Pot Process for the Conversion 5 → 8: Avoidance of the Isolation of 7.** An efficient means to improve a given manufacturing process is doubtless the elimination of the isolation of an intermediate. Such an approach is particularly attractive if the intermediate is questionable from an industrial hygiene point of view. Of course, by omitting the crystallization of epoxide **7**, an outlet for impurities is lost. However, since in the current manufacturing process the conversion from **5** to **7** proceeds quite cleanly, we were confident that from a quality point of view the elimination of the isolation of **7** should be feasible. When we further found that chlorohydrin **6** can be converted directly to **8** at elevated temperature (130−150 °C), we were even more encouraged to proceed toward our envisaged one-pot process. Apparently, not only the isolation but even the formation of epoxide **7** seems to be largely avoidable.[9] Since the direct nucleophilic attack of the amine on chlorohydrin **6** requires harsher conditions than the ring opening of epoxide **7**, a solvent change from ethanol to a higher-boiling solvent was necessitated. In our case, the solvent of choice is the reactant itself, i.e., dibutylamine.

Thus, the new process appears as shown in Scheme 2. For the formation of chlorohydrin **6**, the reaction conditions of the current process could be maintained. After completion of the reduction, instead of sodium methylate, three equivalents of dibutylamine is added to the reaction mixture, and most of the ethanol is distilled off during heating to 140 °C. At this temperature, chlorohydrin **6** is consumed within 2−3 h to form **8**.

***Scheme 2.*** **One-pot process for the conversion 5 → 8**[a]



[a] Reagent and conditions: (a) $NaBH_4$, EtOH, 0−5 °C; (b) dibutylamine, 140 °C, 3 h.

The reaction mixture is cooled to 90 °C, and aqueous sodium hydroxide is added to neutralize the amine salts. After

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(8) The yield of the chlorination can be increased up to 90% when the reaction is run at high concentration in acetonitrile and NCS and hydrochloric acid are used. Perrumattam, J.; Shao, Ch.; Confer, W. L. *Synthesis* **1994**, 1181.

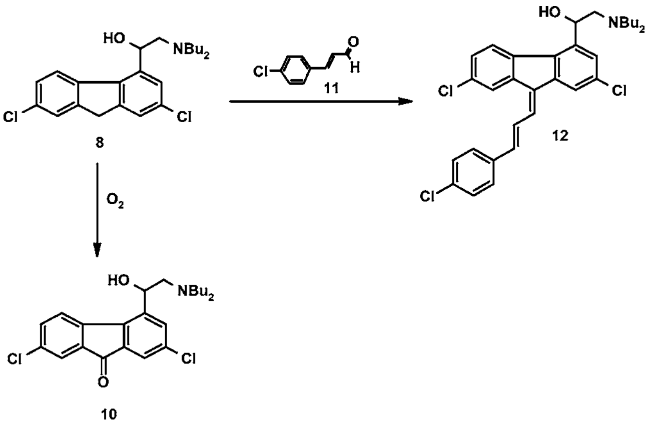
(9) When monitoring the progress of the conversion of **6** to **8**, maximal 1−2% of epoxide **7** could be detected in reaction mixture.

phase separation and washing, dibutylamine is distilled off. The organic layer is cooled to 0 °C, and compound **8** is isolated by filtration and drying. These new process conditions afford amino alcohol **8** in the same quality and yield as for the old process. With the elimination of the intermediate epoxide **7** and the fast conversion **6** → **8**, a significant increase in throughput was also achieved. In addition, sodium methylate was eliminated, and the excess of sodium borohydride was reduced from 1.5 to 1.3 equiv (see Experimental Section).

**3.2. Optimized Process Conditions for the Manufacture of 2.** The condensation of intermediate **8** with *p*-chlorobenzaldehyde in the presence of sodium hydroxide leads in a fast and clean reaction to an approximately 1:1 mixture of *E*-isomer **9** and *Z*-isomer **2**. From this mixture, the desired *Z*-isomer **2** is obtained in reasonably pure form by direct crystallization from the reaction mixture. To realize an optimal yield, isomer **9** must be equilibrated to **2** during the crystallization of compound **2**. For a production process, not only the yield but also the cycle time is of considerable interest. Under the current process conditions, the crystallization was performed at 38 °C, requiring about 30 h for the isomerization and crystallization. Such a long cycle time was in sharp contrast to our idea of having a high throughput process. Since it was not possible to make the process significantly more productive by increasing[10] the concentration, the only way to boost the throughput was to shorten the cycle time for the isomerization and crystallization process. With increasing the temperature and concentration of sodium hydroxide, two obvious options were at hand.

To increase the temperature from the currently used 38 °C would not only certainly increase the rate of this readjustment of the *E/Z* equilibrium but would also lead to a lower yield due to the higher solubility of **2** in the reaction mixture and potentially to the formation of larger amounts of by-products. We were able to solve this optimization problem by altering the temperature profile during the crystallizing process. After completion of the reaction, the mixture was not kept at a constant temperature of 38 °C but heated to 70 °C for maximal 1 h[11] before cooling to 38 °C. As to increasing the amount of sodium hydroxide, an increase from the currently used 0.86 to 2 equiv proved to be optimal.[12] In the course of this investigation we were also able to reduce the excess of *p*-chlorobenzaldehyde from 0.26 to 0.05 equiv. With the combination of these achievements, the optimized temperature profile, the increased amounts of sodium hydroxide, and the slight increase in the concentration, we were able to shorten the cycle time for the isomerization−crystallization process from currently required 30 h to 8 h and to increase the throughput by a factor of about 5.

***Scheme 3.*** **Formation of by-products 10 and 12**



In the current process, the final crystallization of crude **2** is performed in 2-propanol. Due to the relatively low solubility of **2** in boiling 2-propanol, this purification process[13] has to be run in rather low concentration.[14] Thus, the only chance to significantly improve the throughput of the process was to consider a change of solvent. Although reluctant to change solvent in the final crystallization, we felt that in our case this had to be done. Eventually, with heptane we found a solvent in which crude **2** could be dissolved at a 5× higher concentration than in 2-propanol. Heptane also proved to be satisfactory for the depletion of by-products. Fortunately, with the new crystallization procedure in heptane, the physical properties of the isolated product were similar to those of the current process material; thus, no concerns with regard to filtration, drying, and tabletting were to be expected.

**3.3. Optimized Process Conditions and By-product Formation.** With the significant increases in reaction temperature and the concentration of sodium hydroxide, we had not only enhanced the reaction rate for our desired reaction but had also increased the risk of forming more and, even worse, creating new by-products. As to fluorenone **10** (Scheme 3), this compound is formed instantaneously if the reaction mixture comes in contact with oxygen, regardless of whether the current or new reaction conditions are used; by working under inert conditions, its formation can be almost completely suppressed. However, a new by-product was also detected in crude **2**: compound **12**, apparently the condensation product of **8** with *p*-chlorocinnamaldehyde, **11**.[15]

We were somewhat puzzled when we tried to find an explanation for the formation of *p*-chlorocinnamaldehyde, **11**. We had to reject the most plausible rationale, the contamination of *p*-chlorobenzaldehyde with small amounts of **11**.[16] Thus, aldehyde **11** must have been formed during the reaction, most probably via aldol condensation of

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[10] When drastically reducing the amount of solvent, an oily mass rather than a crystalline product is formed, leading to subsequent crust formation; only an increase of concentration of **8** from 5% to 6% was feasible.

[11] To suppress the formation of by-products (see section 3.3), prolonged heating at 70 °C has to be avoided.

[12] The higher concentration of sodium hydroxide has its beneficial effect on the crystallization only in combination with the higher temperature. At 38 °C, no rate-enhancing effect was observed when the amount of sodium hydroxide was increased from 0.86 to 2 equiv.

[13] In addition to some minor compounds, the *E*-isomer **9** at 1−3% is the major by-product in crude **2**.

[14] For 1 kg of crude **2**, 25 L of 2-propanol are required.

[15] When carefully checking the crude reaction mixture of the milder current process, compound **12** can be detected also; however, it is completely removed into the mother liquor during the crystallization process that leads to crude **2**. With the new conditions, more of **12** is formed, and its complete removal occurs in the recrystallization of **2**.

[16] In the *p*-chlorobenzaldehyde we used for these experiments, compound **11** was not detectable by GC or HPLC analytics.

*p*-chlorobenzaldehyde with acetaldehyde. Indeed, compound **12** was formed more dominantly if the reaction **8** → **2** was run in the presence of 0.1 equiv of acetaldehyde. Also, when the reaction was run in 2-propanol instead of ethanol, no traces of **12** were formed, supporting the likelihood that ethanol was the source for acetaldehyde. We could exclude oxygen as the oxidizing agent for ethanol. Irrespective of whether the reaction was run under inert conditions or in the presence of oxygen, compound **12** was formed in similar amounts.[17] Thus, acetaldehyde seemed to be formed in small amounts from ethanol via hydride abstraction by a hydride acceptor, most likely *p*-chlorobenzaldehyde.

Only recently have we encountered a similar hydride transfer while investigating the condensation reaction of the sodium lithium salt of *tert*-butyl acetoacetate with *E*-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-2-propenal in the fluvastatin project.[18] The hydride transfer of electron-rich species to nonenolizable aldehydes has also been reported by other authors.[19]

The formation of by-product **12** cannot be completely prevented. However, by observing the optimal temperature profile during the isomerization−crystallization in the Knoevenagel condensation, it can be maintained at a level low enough that its complete removal is guaranteed during the recrystallization of **2**.

## 4. Summary

The manufacturing process for lumefantrine **2** was reworked. For the conversion of **5** to compound **8** a one-pot process was developed, eliminating isolation of the undesirable epoxide **7**. A significant increase in throughput was also achieved by applying new reaction conditions for the Knoevenagel condensation of **8** to **2** and for the recrystallization of **2**. The elimination of the somewhat increased level of by-product **12** could be brought under control.

## 5. Experimental Section

**5.1. 2,7-Dichloro-9H-fluorene (4).** Chlorine (92 g, 1.30 mol) was passed into the suspension of fluorene (103 g, 0.618 mol) in acetic acid (661 g) at 35−45 °C. While fluorene was dissolving, compound **4** started to crystallize from the mixture. After the addition of chlorine was completed (approximately 15 h), the mixture was heated to 90 °C to liberate formed hydrochloric acid and to dissolve the product. The mixture was cooled to room temperature, and the precipitated product was isolated by filtration and drying to yield 20 g (48%) of pure **4**.

**5.2. 2-Chloro-1-(2,7-dichloro-9H-fluoren-4-yl)ethanone (5).** A mixture of chloroacetyl chloride (41 g, 0.363 mol), $AlCl_3$ (59 g, 0.444 mol), and dichloromethane (118 mL) was cooled to −5 °C. A solution of **4** (69 g) dissolved in dichloromethane (307 mL) was added. After 3−10 h, the deep-red reaction mixture was transferred to 15% aqueous hydrochloric acid (500 mL). After phase separation, the organic phase was washed twice with water. Dichloromethane was distilled off, while ethanol was added at the same rate. The crystallized product was isolated by filtration to give 86 g (94%) of pure **5**.

**5.3. 2-Dibutylamino-1-(2,7-dichloro-9H-fluoren-4-yl)-ethanol (8).** To a slurry of **5** (80 g, 0.257 mol) in ethanol (240 mL) was added sodium borohydride (3.15 g, 0.083 mol) portionwise at −5 to 5 °C within 1 h. As the viscosity increased, good mixing was necessary to reach complete conversion. After agitating for 1 h, dibutylamine (99.6 g, 0.771 mol) was added, and the mixture was heated up to distill off the ethanol. The mixture was heated to 140 °C for 3 h, cooled down to below 90 °C, and quenched with 10% aqueous sodium hydroxide (100 mL). After phase separation, the organic phase was washed with brine (2 × 100 mL). The organic layer was concentrated under reduced pressure at 60−90 °C. After complete removal of dibutylamine, ethanol (170 mL) was added, keeping the temperature above 60 °C. The solution was seeded at 50 °C and allowed to crystallize at 0 °C to yield 84.5 g (81%) of pure **8**.

**5.4. 2-Dibutylamino-1-{2,7-dichloro-9-[1-(4-chlorophenyl)meth-(*Z*)-ylidene]-9H-fluoren-4-yl}ethanol (2).** *New Process Conditions.* A stirred mixture of **8** (80 g, 0.197 mol), *p*-chlorobenzaldehyde (29 g, 0.207 mol), sodium hydroxide (15.8 g, 0.394 mol), and ethanol (1160 mL) was heated up within 1 h from 23 to 70 °C and immediately afterwards cooled within 1 h from 70 to 38 °C. The mixture was agitated at 38 °C for at least 4 h to complete crystallization. After filtration, washing, and drying, 91.6 g (88%) of crude **2** was isolated. When the reaction was run in the presence of oxygen, compound **10** was obtained as the main product and was isolated in crude form by silica gel chromatography. $^1$H NMR (400 MHz, chloroform-*d*) $\delta$ 0.98 (t, $J = 7.23$ Hz, 6 H), 1.30−1.57 (m, 8 H), 2.43−2.58 (m, 3 H), 2.64−2.73 (m, 2 H), 2.82 (dd, $J = 12.95, 3.60$ Hz, 1 H), 5.16 (dd, $J = 10.23, 3.54$ Hz, 1 H), 7.45 (d, $J = 1.39$ Hz, 2 H), 7.55 (d, $J = 2.08$ Hz, 1 H), 7.65 (t, $J = 1.26$ Hz, 1 H), 7.80 (dd, $J = 2.08, 0.57$ Hz, 1 H); MS (ES$^+$) *m*/*z* 420 (MH$^+$).

**5.5. New Process for the Crystallization of 2.** A mixture of crude **2** (15 g, 0.284 mol) and heptane fraction (75 mL) was heated to reflux (94 °C). A solution was formed which was clear filtered above 90 °C. The solution was cooled to 70 °C, seeded with pure **2**, cooled within 4 h to 3 °C, and stirred at that temperature for at least 1 h. The suspension was filtered, washed, and dried to yield 13.9 g (93%) of pure **2**.

**5.6. Preparation of Compound 12.** A stirred mixture of **8** (8.2 g, 20 mmol), *p*-chlorocinnamaldehyde **11** (3.0 g, 21.1 mmol), sodium hydroxide (0.69 g, 17.3 mmol), and ethanol (159 mL) was heated up within 1 h from 23 to 38 °C. The mixture was agitated at 38 °C for 18 h. The formed crystals were isolated by filtration and recrystallized from ethyl acetate and hexane. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.79

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[17] This is in sharp contrast to the formation of fluorenone **10**. Compound **10** can be made to the dominant product if during the conversion of **8** → **2** air is bubbled through the reaction mixture.

[18] Fuenfschilling, P. C.; Hoehn P.; Mutz J.-P. *Organic Process Res. Dev.* **2007**, *11*, 13.

[19] For lithium enolate of acetaldehyde as the reducing agent for nonenolizable aldehydes, see: Di Nunno, L.; Scilimati, A. *Tetrahedron* **1988**, *44*, 3639.

(t, $J = 7.15$ Hz, 6 H), 1.13−1.21 (m, 4 H), 1.21−1.31 (m, 4 H), 2.37−2.45 (m, 2 H), 2.46−2.54 (m, 2 H), 2.62 (dd, $J = 13.20, 6.60$ Hz, 1 H), 2.69−2.79 (m, 1 H), 5.28 (t, $J = 5.69$ Hz, 1 H), 5.41 (br s, 1 H), 7.26 (d, $J = 15.04$ Hz, 1 H), 7.46 (d, $J = 8.44$ Hz, 1 H), 7.50 (s, 1 H), 7.51 (d, $J = 7.70$ Hz, 2 H), 7.78 (d, $J = 12.10$ Hz, 1 H), 7.86 (d, $J = 8.44$ Hz, 2 H), 7.99 (dd, $J = 14.67, 12.10$ Hz, 1 H), 7.97 (s, 1 H), 8.06 (d, $J = 8.44$ Hz, 1 H), 8.33 (s, 1 H); MS (ES$^+$) *m*/*z* 554 (MH$^+$).

## Acknowledgment

We thank B. Bianchi, L. Hueber, P. Schorter, and S. Tardino for their enthusiastic support of this work. In particular, we thank also Thomas Kuhn, Global Project Leader for Coartem, for his highly appreciated support during the whole duration of this project.

Received for review November 21, 2006.

OP060244P